(FILE 'HOME' ENTERED AT 17:17:05 ON 01 SEP 2004)

FILE 'MEDLINE, CANCERLIT' ENTERED AT 17:17:55 ON 01 SEP 2004

L1	0	S	E2F1 PROMOTER AND ADENOVIRAL AND PRB
L2	0	S	E2F1 PROMOTER AND ADENOVIRAL
L3	0	S	E2F PROMOTER AND ADENOVIRAL AND PRB
L4	21	S	CR2 AND E1A AND E2F
L5	11		DUP REM L4 (10 DUPLICATES REMOVED)
L6	1692226	S	TUMOR OR CANCER
L7	4072	S	E2F1 OR E2F
L8	1328	S	L7 AND PROMOTER
L9	628	S	L8 AND L6
L10	112	S	L9 AND ADENOVIR?
L11	60	S	L10 AND E1A
L12	33		DUP REM L11 (27 DUPLICATES REMOVED)

L12 ANSWER 2 OF 33 MEDLINE on STN
AN 2003154263 MEDLINE
DN PubMed ID: 12670895
TI An oncolytic **adenovirus** selective for retinoblastoma **tumor** suppressor protein pathway-defective tumors: dependence on **E1A**, the **E2F**-1 **promoter**, and viral replication for selectivity and efficacy.
AU Jakubczak John L; Ryan Patricia; Gorziglia Mario; Clarke Lori; Hawkins Lynda K; Hay Carl; Huang Ying; Kaloss Michele; Marinov Anthony; Phipps Sandrina; Pinkstaff Anne; Shirley Pamela; Skripchenko Yelena; Stewart David; Forry-Schaudies Suzanne; Hallenbeck Paul L
CS Genetic Therapy, Inc, Gaithersburg, Maryland 20878, USA.
SO Cancer research, (2003 Apr 1) 63 (7) 1490-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030403
Last Updated on STN: 20030423
Entered Medline: 20030422
AB The use of oncolytic **adenoviruses** as a **cancer** therapeutic is dependent on the lytic properties of the viral life cycle, and the molecular differences between **tumor** cells and nontumor cells. One strategy for achieving safe and efficacious **adenoviral** therapies is to control expression of viral early gene(s) required for replication with **tumor**-selective **promoter**(s), particularly those active in a broad range of **cancer** cells. The retinoblastoma **tumor** suppressor protein (Rb) pathway is dysregulated in a majority of human cancers. The human **E2F**-1 **promoter** has been shown to be selectively activated/derepressed in **tumor** cells with a defect in the Rb pathway. Ar6pAE2fE3F and Ar6pAE2fF are oncolytic **adenoviral** vectors (with and without the viral E3 region, respectively) that use the **tumor**-selective **E2F**-1 **promoter** to limit expression of the viral **E1A** transcription unit, and, thus, replication, to **tumor** cells. We demonstrate that the antitumor activity of Ar6pAE2fF in vitro and in vivo is dependent on the **E2F**-1 **promoter** driving **E1A** expression in Rb pathway-defective cells, and furthermore, that its oncolytic activity is enhanced by viral replication. Selective oncolysis by Ar6pAE2fF was dependent on the presence of functional **E2F** binding sites in the **E2F**-1 **promoter**, thus linking antitumor viral activity to the Rb pathway. Potent antitumor efficacy was demonstrated with Ar6pAE2fF and Ar6pAE2fE3F in a xenograft model following intratumoral administration. Ar6pAE2fF and Ar6pAE2fE3F were compared with Addl1520, which is reported to be molecularly identical to an E1B-55K deleted vector currently in clinical trials. These vectors were compared in in vitro cytotoxicity and virus production assays, after systemic delivery in an in vivo **E1A**-related hepatotoxicity model, and in a mouse xenograft **tumor** model after intratumoral administration. Our results support the use of oncolytic **adenoviruses** using **tumor**-selective **promoter**(s) that are activated or derepressed in **tumor** cells by virtue of a particular defective pathway, such as the Rb pathway.

L12 ANSWER 19 OF 33 CANCERLIT on STN
AN 1998641306 CANCERLIT
DN 98641306
TI Mechanism of action of the Rb **tumor** suppressor (Meeting abstract).
AU Anonymous
CS Washington University School of Medicine, St. Louis, MO 63110.
SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 648.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199807
ED Entered STN: 19980713
Last Updated on STN: 19980713
AB The retinoblastoma protein (Rb) is a **tumor** suppressor that regulates progression from G1 to S phase of the cell cycle. Rb is a transcriptional repressor selectively targeted to promoters through interaction with the **E2F** family of cell cycle transcription factors. When Rb is tethered to **promoter** through **E2F**, it blocks **E2F** activity and binds surrounding transcription factors, preventing their interaction with basal transcription complex, and thus inhibiting cell cycle gene transcription. The Rb-**E2F** interaction was examined by transfecting a mutant form of **E2F**-1 lacking transactivation domain and Rb binding site but retaining the DNA binding domain. This dominant-negative form of **E2F**-1 transformed rat embryo fibroblasts, suggesting: (1) the transactivating domain of **E2F**-1 is not required for cells to progress from G1 to S phase; (2) repressor activity of Rb, bound to **E2F**, regulates G1/S transition. Additionally, we found that this dominant-negative form of **E2F**-1 prevented growth suppression by p16 **tumor** suppressor protein. p16 is a cyclin dependent kinase (cdk) inhibitor that blocks the activity of D cyclins in complex with cdk 4 or 6. Cdk4/6 in complex with D cyclins can phosphorylate and inactivate Rb, allowing progress from G1 to S. Our results suggest that Rb-**E2F** may be the ultimate target of p16 in cells. Two domains in the Rb pocket, A and B, conserved across species and in the Rb-related proteins p107 and p130, are both required for repressor activity. The non-conserved spacer separating A and B is not required. Neither A nor B alone had repressor activity, but repressor activity was observed when the domains were coexpressed on separate proteins. Transfection assays suggest one domain can recruit the other to the **promoter** to form a repressor motif that can both interact with **E2F** and have a dominant inhibitory effect on transcription. A and B interact directly, and mutations disrupting this interaction inhibit repressor activity. The Rb pocket was originally defined as the binding site for oncoproteins from DNA **tumor** viruses such as **adenovirus E1a**. We have found that **E1a** interacts with a site formed by the interaction of A and B, and that this interaction with A and B induces or stabilizes A-B interaction. The A-B repressor motif is shared by Rb-related protein p107. Phosphorylation of Rb by G1 cdks inactivates the protein, allowing cells to progress from G1 to S phase. The A-B interaction forming the repressor motif is blocked by G1 cdk phosphorylation, blocking repressor activity. This A-B repressor motif is the first example of a cdk-regulated transcriptional repressor.

L12 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 3
AN 2002344096 MEDLINE
DN PubMed ID: 12086848
TI Selectively replicating **adenoviruses** targeting deregulated **E2F** activity are potent, systemic antitumor agents.
AU Johnson Leisa; Shen Annie; Boyle Larry; Kunich John; Pandey Kusum; Lemmon Marilyn; Hermiston Terry; Giedlin Marty; McCormick Frank; Fattaey Ali
CS Onyx Pharmaceuticals, Richmond, California 94806, USA.. ljohnson@exelixis.com
SO Cancer cell, (2002 May) 1 (4) 325-37.
Journal code: 101130617. ISSN: 1535-6108.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020628
Last Updated on STN: 20020726
Entered Medline: 20020725
AB We have engineered a human **adenovirus**, ONYX-411, that selectively replicates in human **tumor** cells, but not normal cells, depending upon the status of their retinoblastoma **tumor** suppressor protein (pRB) pathway. Early and late viral gene expression as well as DNA replication were significantly reduced in a functional pRB-pathway-dependent manner, resulting in a restricted replication profile similar to that of nonreplicating **adenoviruses** in normal cells both in vitro and in vivo. In contrast, the viral life cycle and **tumor** cell killing activity of ONYX-411 was comparable to that of wild-type **adenovirus** following infection of human **tumor** cells in vitro as well as after systemic administration in **tumor** -bearing animals.